CHAPTER III

CHEMICAL NOMINATION AND SELECTION

The chemical nomination and selection process is integral to the effective operation and success of the NTP with respect to the testing of chemicals using current methodologies, the validation of new testing methodologies, and for the evaluation of new concepts of mechanisms of toxicity. From its inception, the NTP has had an open nomination process. A number of open calls for chemical nominations have been made, in which individuals from academia, various state and Federal government agencies, labor unions, industry, and the general public were requested to nominate chemicals. The Program regularly publishes for public comment in the *Federal Register* and in the NTP Liaison Office newsletter a listing of chemicals being considered for study. A broad range of regulatory and toxicologic concerns are addressed during the nomination and selection process through the participation of representatives from Federal agencies concerned with public health issues. In addition, representatives from non-government organizations, including industry, labor, and public interest, sit on the NTP Board of Scientific Counselors, and thus have input into chemical selection decisions. Comprehensive presentations will be made to the NTP Board at their meeting on December 13, 1996, about the nomination and selection process by staff of NTP participating agencies, including NIEHS, FDA, NIOSH, NCI, EPA, and OSHA. The Board will be asked to suggest ways the process could be improved as well as provide insight into databases, especially for human toxic effects, that the NTP may have overlooked or not been aware of.

Increased efforts continue to be focused on: (1) improving the quality of the nominations of chemicals, environmental agents, or issues for study; (2) broadening the base and diversity of nominating organizations and individuals; and (3) increasing nominations for endpoints of toxicity other than carcinogenesis.

Chemicals may be studied for a variety of health-related effects, including but not limited to, reproductive and developmental toxicity, genotoxicity, immunotoxicity, metabolism and disposition, as well as carcinogenicity. Further, particular assistance is sought with the selection of studies that permit testing of hypotheses to enhance the predictive

ability of NTP studies, address mechanisms of toxicity, or identify significant gaps in our knowledge of the toxicity of chemicals or classes of chemicals.

Through the NTP Office of Chemical Nomination and Selection, located within the ETP, NIEHS, NTP staff are taking a proactive approach to identify nominations for study by examining lists of high production volume chemicals, toxic release inventories, and exposure indexes. Other approaches have included reviewing available lists of chemicals found in human tissues and reviewing all chemicals testing positive in the *Salmonella* mutagenesis assay that have not been studied in a two-year carcinogenesis bioassay.

The FDA has a formal nomination and selection process from which nominations are submitted to the NTP. The FDA selects chemicals and agents (human or animal drugs, biologics, biomaterial, human and animal food additives, and chemicals used in cosmetics) through its Chemical Selection Working Group (CSWG). The FDA CSWG is composed of one senior scientist from each product Center (Center for Food Safety and Applied Nutrition, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, and Center for Devices and Radiological Health), the Office of Orphan Products Development, the Office of Regulatory Affairs, and the National Center for Toxicological Research. Chemical/agent summaries from each CSWG member who wishes to have consideration for NTP nominations are presented to the working group for discussion. The CSWG membership selects both priority and routine chemicals/agents based upon scientific and regulatory needs. The FDA's NTP Liaison, who serves as the CSWG Chair, prepares and submits all nomination letters to the NTP on behalf of the Agency. (CONTACT PERSON: Dr. W. T. Allaben, NCTR)

The following discussion summarizes the current NTP chemical nomination and selection process, and is followed by a description of accomplishments during FY 1996 and program plans for FY 1997. The process is shown schematically in Figure 6. (CONTACT PERSON: Dr. E. Zeiger, NIEHS)

NTP Chemical Nomination — Member agencies of the National Toxicology Program (FDA, NIEHS, and NIOSH) and other sources (including other Federal agencies, state agencies, the public, labor, and industry) submit nominations of chemicals to the NTP for toxicologic testing. Chemical nominations received during FY 1996, along with CAS Numbers, nomination source, and suggested types of testing, are listed in Table 1 (Appendix A). The nominating sources are asked to also identify: the particular toxicologic informa-

tion needed; the rationale for the nomination; any available background data on production, use, exposure, environmental occurrence; and the extent of available toxicological information (Table 2, Appendix A). However, it is recognized that all potential nomination sources do not have the resources to obtain all the requested information. Therefore, all nominations are considered regardless of the extent of the information submitted. *Nominations should be addressed to NTP Nominations Faculty, c/o Dr. E. Zeiger, National Toxicology Program, NIEHS, MD WC-05, P.O. Box 12233, Research Triangle Park, N.C., 27709.*

Evaluation of Nominated Chemicals — Nominated chemicals are reviewed by the NTP Nominations Faculty to determine whether they have been adequately tested or have been previously considered by the NTP. For chemicals not eliminated from consideration or deferred at this stage, the available literature is examined in detail to prepare Toxicological Summaries which evaluate and summarize the relevant data for each chemical. Included in each Toxicological Summary are: chemical and physical information; production levels; use and exposure categories and levels; regulatory status; toxicological effects; and rationale for the nomination.

The Toxicological Summaries are distributed to the Interagency Committee for Chemical Evaluation and Coordination (ICCEC), composed of representatives from the Agency for Toxic Substances and Disease Registry, Consumer Product Safety Commission, Department of Defense, Environmental Protection Agency, Food and Drug Administration's National Center for Toxicological Research, Occupational Safety and Health Administration, National Cancer Institute, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health, and the National Library of Medicine.

ICCEC members are assigned as reviewers for each chemical after consideration of the nature of its uses and exposure so that, to the extent possible, appropriate regulatory concerns will be addressed. Members are requested to identify their agency's interests, if any, in the chemical, and to search databases unique to their agencies for further information on the nominated chemicals and structurally related substances. During the evaluation, the NTP works actively with regulatory agencies and interest groups to supplement the information about chemicals nominated and to ensure that the chemical

selection process meets regulatory agency needs. Where appropriate, a representative of the nominating organization attends the ICCEC meeting to present the testing needs and answer questions concerning the rationale for the nomination.

At its meeting to consider the nominated chemicals, the ICCEC assigns testing priorities, and also may make recommendations for study in addition to those requested by the nominator. The testing recommendations are based upon whether the chemical satisfies one or more of the NTP chemical nomination guidelines (Table 3, Appendix A). Chemical selection also may incorporate mechanistic considerations in order to study chemicals that may add to an overall understanding of mechanisms of chemical toxicity, species-to-species extrapolation and dose-response relationships. Chemicals are also considered that are part of special initiatives such as the Clean Air Act and "Superfund," and those specifically identified as farm chemicals. Following the ICCEC meeting, the Toxicological Summaries are revised as needed for the accepted chemicals and the ICCEC recommendations are also incorporated. (CONTACT PERSON: Dr. E. Zeiger, ETP, NIEHS)

Public Comment — A *Federal Register* notice listing the chemicals reviewed by the ICCEC and the recommended studies is published. The notice solicits comments from interested parties including information on completed, ongoing, or planned testing in other government organizations and the private sector. These steps enable other individuals and groups to provide data useful to the NTP chemical evaluation and testing process. To ensure broader dissemination, copies of the notice are distributed to the NTP mailing list which includes some 8,000 persons or organizations who have requested to be on the list.

Review and Approval of Nominations — Summaries of the ICCEC's reviews and public comments on the nominated chemicals are then presented to the NTP Board of Scientific Counselors. The Board's comments and pertinent public comments are incorporated into recommendations that are submitted to the NTP Executive Committee. This Committee reviews and approves the decision on whether to test, defer, or delete each of the nominated chemicals for the various types of study, and recommends priorities for testing.

Implementation of Testing Recommendations — Following Executive Committee action, each chemical is assigned to an NIEHS, FDA, or NIOSH staff scientist (project

leader) who assesses the data compiled during the chemical evaluation process and other information obtained from detailed searches of the published literature and public comments. The project leader also consults with industrial sources on such issues as mode of production, uses, worker exposure, planned or ongoing testing, and availability of the chemical for study. The project leader, often in collaboration with a project review team which can include representatives of the nominating agency, can develop a study plan to address the research needs, or can return the chemical to the Executive Committee with a recommendation not to pursue study. Such a recommendation may be based upon technical difficulties in studying the chemical, its lack of availability, or the existence of adequate outside testing. If a study is warranted, the project leader, with approval of the project team, presents a study proposal to an NIEHS/NTP project review committee. This committee, which consists of scientists representing different scientific disciplines, is responsible for seeing that the project plan addresses all the issues of scientific concern, and will be carried out by the most appropriate methods (contracts, grants, etc.). All chemicals selected as a result of this process are then studied as time and resources permit.

Results of toxicological studies of selected chemicals are routinely peer-reviewed. The results are published as NTP Technical Reports and/or in the open scientific literature. Test results are also available from the NTP subsequent to peer-review but prior to publication.

Chemical Nomination and Selection Activities

Evaluation of Nominated Chemicals — During FY 1996, the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) reviewed 11 chemicals that were previously nominated to the Program and made recommendations based in part upon whether the chemical satisfied one or more of the eight nomination guidelines. These chemicals were evaluated by the ICCEC on July 15, 1996.

Review and Approval of Nominations — On January 26, 1996, the NTP Executive Committee reviewed and approved ICCEC recommendations on 11 chemicals nominated to the NTP for extensive toxicological characterization and evaluated by the ICCEC on September 28, 1995. Six of the chemicals— allyl bromide, cellulose insulation, cyanogen

chloride, diazoaminobenzene, dimethylaminopropyl chloride Hcl, and Stoddard solvent—were recommended by the ICCEC for study, while one, isopropenyl acetate, was recommended for no testing. Four chemicals were reviewed and deferred for further action -- chlorate, 1-octene, phenyl glyoxal, and pyridostigmine bromide.

On August 1, 1996, the Executive Committee reviewed and approved ICCEC recommendations on 11 chemicals nominated to the NTP for extensive toxicological characterization and evaluated by the ICCEC on July 15, 1996. Six of the chemicals -- chlorate, dibromoacetic acid, carbonyl sulfide, cumene, 1,2-dibromo-2,4-dicyanobutane, and melatonin -- were recommended by the ICCEC for study. Two chemicals were recommended for deferral -- *tert*-butyl formate and 2,4,6-tribromophenol. Three chemicals previously approved -- 12-O-hexadecanoyl-16-hydroxyphorbol-13-acetate (HHPA), methanol, and 1-octene -- were recommended for no testing. The chemicals, nomination sources, and testing or no testing recommendations are given in Table 4 (Appendix A). (CONTACT PERSON: Dr. E. Zeiger, ETP, NIEHS)